of Office Action, mailed 11/20/02). Applicants maintain that the Examiner's assertion regarding this statement is incorrect. The text appearing on page 2, line 28 through page 3, line 3 of the specification is reproduced below,

> Following a traumatic injury to the central nervous system, *a cascade of physiological events* leads to neuronal loss including, for example, an inflammatory immune response and excitotoxicity resulting from the initial impact disrupting the glutamate, acetylcholine, cholinergic, $GABA_A$, and NMDA receptor systems. In addition, the traumatic CNS injury is frequently followed by brain and/or spinal cord edema that enhances the cascade of injury and leads to further secondary cell death and increased patient mortality. (emphasis added)

As expressly stated in the paragraph, a traumatic injury to the central nervous system leads to *a cascade of physiological events which lead to neuronal loss*. This point is again expressed in the specification on page 5, lines 8-15 that clearly states that "a traumatic injury to the CNS results in *multiple physiological events* that impact the extent and rate of neurodegeneration and thus the final outcome of the injury". While the specification discusses that the $GABA_A$ receptor systems may play a role in a traumatic injury to the CNS, it is hardly the only physiological event leading to the neuronal damage. In the Office Action, the Examiner maintains his position regarding this statement and appears to simply be selecting words from the specification that support his position and using them to put forth a scientific theory that is not disclosed in the specification. The Examiner is respectfully requested to withdraw the assertion that Applicants have made the alleged admission.

Moreover, "[W]hen an Examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory must be provided." (See MPEP 2144.02). Furthermore, if the Examiner is basing evidence for this theory on facts within his personal knowledge, an affidavit must be provided. (See MPEP 2144.03). Therefore, if the Examiner maintains his position regarding the scientific conclusion, the Examiner is respectfully requested to provide scientific evidence for his theory that traumatic brain injury to the CNS is "tightly" associated with GABA.

Second, the Examiner further asserts that "the claiming of a new use, new function or unknown property which is inherently present in the prior art will not make the claim nonobvious." Applicants submit that the claims of the instant invention are not inherently taught by any of the cited references. Gee *et al.* suggests methods of modulating brain excitability to alleviate stress, anxiety, and seizure activity. However, the claims of the instant invention are drawn to "a method of treating a *traumatic central nervous system injury*" (claims 1-15), and "a method of decreasing neurodegeneration on a population of cells in a subject *following a traumatic injury to the central nervous system*" (claims 16-20). As stated on page 6, lines 17-23 of the specification, "[a] traumatic injury to the CNS is characterized by a *physical impact* to the central nervous system" (emphasis added). Gee *et al.* does not teach or suggest administering any progesterone metabolite to a subject following a traumatic injury (i.e., physical impact) to the CNS. Moreover, the Roof *et al.* references teach only the administration of progesterone and offer no suggestion that the progesterone metabolite allopregnanolone would be successful. As the art never taught or suggested the administration of allopregnanolone to a subject having a *traumatic* CNS injury, the claims of the instant invention are not inherently taught or rendered obvious by the cited reference.

The Examiner further maintains a *prima facie* case of obviousness in view of "Applicants Admissions", Roof et al. (1994) *Experimental Neurology 129*:64-69; Roof *et al.* (1992) *Restorative Neurology and Neuroscience 4*:425-427; and Gee *et al.* (U.S. Patent No. RE35,517). Applicants respectfully traverse and maintain that a *prima facie* case of obviousness has not been established.

First, as discussed above, Applicants have *not* admitted that a tight association exits between GABA and a traumatic central nervous system injury.

Second, a *prima facie* case of obviousness requires a motivation to combine the references. The Examiner states that the motivation to combine the references is based on his belief that Gee *et al.* supports the conclusion that allopregnanolone has "the same therapeutic usefulness as progesterone in [the] CNS" (emphasis added, Office Action dated November 20, 2002). However, Gee *et al.* does not support this position. In fact, Gee *et al.* teaches that

progesterone and its various metabolites have varying binding activity for the GBR complex. See Table 2 that ranks various metabolites (including progesterone and allopregnanolone) in their order of potency and efficacy at the GBR complex. In fact, Gee *et al.* conclude that "progesterone has very low potency at the GBR complex" compared to some of its metabolites (see column 17, lines 24-28). Accordingly, the art does not recognize that allopregnanolone and progesterone have the "the same therapeutic usefulness" as asserted in the Office Action.

As made of record in the Response file August 23, 2002, Applicants maintain that there would be no motivation to combine Gee *et al.* with Roof *et al.* (1992), Roof *et al.* (1994) and Roof *et al.* (1997). ***The prior art itself must provide the skilled artisan the motivation to make the claimed invention.*** Applicants continue to maintain the claims of the present invention are being used as a guide to select references at random that mention various aspects of the claimed invention. Gee *et al.* (RE. 35,517) provide methods for modulating brain excitability to alleviate stress, anxiety, and seizure activity using certain progesterone derivatives. Gee *et al.* provide no teaching or suggestion that any progesterone derivative could be successfully used to treat a *traumatic* CNS injury. While the Roof *et al.* references teach the administration of progesterone to rats following a frontal contusions, none of these references by Roof *et al.* disclose or suggest the administration of allopregnanolone to treat a traumatic CNS injury or reduce neurodegeneration following a traumatic CNS injury. Moreover, as discussed in further detail above, Gee *et al.* teach that progesterone has different receptor activity than that of its metabolites. And finally, there was no suggestion that any of the compounds disclosed would have activity in the treatment of traumatic CNS injury. A traumatic CNS injury produces multiple physiological events that lead to neurodegeneration. None of the cited references would guide one of skill in the art to select allopregnanolone, among the multitude of progesterone metabolites, and administer this compound to a subject having a *traumatic* CNS injury.

Moreover, on page 5 of the Office Action dated November 20, 2002, the Examiner further asserts that since Examples 6 and 7 of the present application administer progesterone, the "Applicant clearly acknowledges that progesterone and its particular metabolite, allopregnanolone, have the same therapeutic usefulness". ***Applicants never stated or suggested that progesterone and allopregnanolone had the same therapeutic usefulness.*** The examples

using progesterone simply provide further evidence of the activity of progesterone on behavior and lesion size, and the use of a cyclodextrin vehicle in administration. These experiments do not indicate that the results should be extrapolated to allopregnanolone. Examples 6 and 7 do not represent examples of the invention presently being claimed, and the Examiner is respectfully requested to withdraw his assertion regarding Applicant's admission.

For all of these reasons, Applicants maintain that the art cited by the Examiner does not provide the motivation to combine the reference. The law is clear that without motivation to combine the references, a rejection under 35 USC §103 fails.

Third, a *prima facie* case of obviousness requires that cited prior art to provide a reasonable expectation of success. Applicants maintain that the art fails to provide a reasonable expectation that the administration of allopregnanolone to a subject would successfully treat a *traumatic* CNS injury or decrease neurodegeneration following a *traumatic* CNS injury as claimed by the instant invention. First, the guidance provided by the cited art must be sufficiently specific to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the claimed invention. None of the references cited demonstrate or suggest the administration of allopregnanolone to treats a *traumatic* CNS injury or decrease neurodegeneration following a *traumatic* CNS injury as claimed by the instant invention. The art therefore fails to inherently or explicitly suggest the administration of allopregnanolone to a subject having a *traumatic* (i.e., physical force) CNS injury. Moreover, the initial impact of a traumatic injury to the CNS produces many physiological events, including the disruption of multiple receptors/neurotransmitters. Therefore modulating the activity of a single receptor as taught by Gee *et al.* is hardly sufficient to provide a reasonable expectation that allopregnanolone would successfully treat the traumatic CNS injury as claimed by the instant invention. Consequently, the prior art offers no suggestion or expressed expectation that administration of allopregnanolone would successfully treat a traumatic brain injury.

As explained in the previous Response, pages 20-32 of the specification demonstrates for the first time that following a traumatic central nervous system injury, the administration of allopregnanolone significantly reduces cerebral edema when compared to control rats (see Figure 1); significantly increases the learning rate compared t control rats (See Figure 2); and,

significantly delays the synthesis and level of activity of inflammatory cytokines (Figures 3 and 4). The Examiner, however, states that the results set forth in the specification of the instant invention are "clearly expected and not unexpected based on the cited prior art" and therefore concludes that a reasonable expectation of success exists. The Examiner is reminded that one cannot base obviousness upon what a person skilled in the art might try or might find obvious to try but rather must consider what the prior art would have led a person skilled in the art to do. As discussed above, Gee *et al.* teaches that progesterone and its metabolites have varying activity and offer no teaching that allopregnanolone could treat a *traumatic* injury to the CNS. Similarly, Roof *et al.* only teach the administration of allopregnanolone following a frontal contusion. Prior to the present invention, one of skill in the art would not have recognize that allopregnanolone could be used to treat a traumatic CNS injury or decrease neurodegeneration as claimed by the present invention. Therefore, contrary to the Examiner's assertion, there was not a reasonable chance of success.

In summary, Applicants maintain a *prima facie* case of obviousness has not been established. Applicants respectfully submit that the claimed methods are not obvious in view of the cited references and respectfully request that the rejection of claims 1-20 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSIONS

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Filed:	October 9, 2001	Examiner:	Shaojia A. Jiang
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